DR. MARGHERITA BARBUTI (Orcid ID : 0000-0003-0077-3815)
DR. EDUARD VIETA (Orcid ID : 0000-0002-0548-0053)

Article type : Original Article

The role of different patterns of psychomotor symptoms in major depressive episode: pooled analysis of the BRIDGE and BRIDGE-II-MIX cohorts

Running head: Psychomotor symptoms in major depressive episode.

Margherita Barbuti[1], Cecilia Mainardi[1,2], Isabella Pacchiarotti[2], Norma Verdolini[2,3,4,5], , Giuseppe Maccariello[1], Jules Angst[6], Jean-Michel Azorin[7], Charles L. Bowden[8], Sergey Mosolov[9], Allan H. Young[10], Eduard Vieta[2], Giulio Perugi[1] for the BRIDGE and the BRIDGE-II-Mix Study Group.

[1]Department of Experimental and Clinic Medicine, Section of Psychiatry, University of Pisa, Italy;

[2]Bipolar Disorders Unit, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Catalonia, Spain;

[3]Division of Psychiatry, Clinical Psychology and Rehabilitation, Santa Maria della Misericordia Hospital, University of Perugia, Italy;

[4]FIDMAG Germanes Hospitalàries Research Foundation, c/ Dr. Pujades, Barcelona, Catalonia, Spain;

[5]CIBERSAM, Centro Investigación Biomédica en Red Salud Mental, Barcelona, Spain;

[6]Psychiatric Hospital, University of Zurich, Switzerland;

[7]AP HM, Psychiatric Pole, Sainte Marguerite, Marseille, France;

[8]Department of Psychiatry, University of Texas Health Science Center at San Antonio, TEXAS, USA;

[9]Department for Therapy of Mental Disorders, Moscow Research Institute of Psychiatry, Moscow, Russia;

[10]Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London & South London and Maudsley NHS Foundation Trust, Denmark Hill, Camberwell, London SE5 8AZ, UK.

Corresponding author

Prof. Eduard Vieta,

Bipolar Disorders Unit, Institute of Neuroscience, IDIBAPS, CIBERSAM, Hospital Clínic de Barcelona.

Villarroel, 170, 08036, Barcelona, Catalonia, Spain.

Email: evieta@clinic.cat

Abstract

Background: psychomotor agitation (PA) or retardation (PR) during major depressive episodes (MDEs) have been associated with depression severity in terms of treatment-resistance and course of illness.

Objectives: we investigated the possible association of psychomotor symptoms (PMSs) during a MDE with clinical features belonging to the bipolar spectrum.

Methods: the initial sample of 7689 MDE patients was divided into three subgroups based on the presence of PR, PA and non-psychomotor symptom (NPS). Univariate comparisons and multivariate logistic regression models were performed between subgroups.

Results: 3720 patients presented PR (48%), 1971 shown PA (26%) and 1998 had NPS (26%). In the PR and PA subgroups, the clinical characteristics related to bipolarity, along with the diagnosis of Bipolar Disorder (BD), were significantly more frequent than in the NPS subgroup. When comparing PA and PR patients, the former presented higher rates of bipolar spectrum features, such as family history of BD (OR=1.39, CI=1.20-1.61), manic/hypomanic switches with antidepressants (OR=1.28, CI=1.11-1.48), early onset of first MDE (OR=1.40, CI=1.26-1.57), atypical (OR=1.23, CI=1.07-1.42) and psychotic features (OR=2.08, CI=1.78-2.44), treatment with mood-stabilizers (OR=1.39, CI=1.24-1.55), as well as a BD diagnosis according to both the DSM-IV criteria and the bipolar specifier criteria. When logistic regression model was performed, the clinical features that significantly differentiated PA from PR were early onset of first MDE, atypical and psychotic features, treatment with mood-stabilizers and a BD diagnosis according to the bipolar specifier criteria.

Conclusions: PMSs could be considered as markers of bipolarity, illness severity, and treatment complexity, particularly if PA is present.

Keys words: psychomotor agitation, psychomotor retardation, bipolar disorder, major depressive episode.

Introduction

Psychomotor Symptoms (PMSs) have been considered as core features in the psychopathology of mood disorders and proved to have both diagnostic and prognostic values in major depression [1,2]. PMSs remain fundamental signs in contemporary classifications of mental disorders and are included among the diagnostic criteria for Major Depressive Episodes (MDEs) in both DSM-5 and ICD-11. However, despite the clear neurophysiological differences between agitated and retarded depression, there is no distinction between the two patterns in such classifications. This approach has remained unchanged over the last 40 years although clinical findings clearly indicate the heterogeneity of depressive disorders [2].

Parker and colleagues highlighted that PMSs should be considered the fundamental symptomatological characteristic of melancholia. They also found that the severity of PMSs has predictive value with regard to treatment outcome with electroconvulsive therapy (ECT) and tricyclic antidepressants (ADs) rather than selective narrow-action AD medications (e.g., serotonin uptake inhibitors) [3]. However, the association between PMSs and melancholia may be partly tautological, and the linkage to treatment outcome could conceivably be associated with items influenced by melancholic manifestations that do not reflect psychomotor disturbance (e.g., cognitive and neuro-vegetative symptoms).

Psychomotor retardation (PR) has been reported as a major feature of depression, in particular in the melancholic subtype. PR was also found to be associated with bipolarity and with conversion from unipolar to bipolar depression in prospective follow-up. In this sense, PR might be an indicator of bipolarity in depressed patients [4]. Nevertheless, several studies did not find differences in the rates of PR between major depressive and bipolar II disorder samples, but rather significantly higher rates of agitation among the group with bipolar II disorder [5].

The concomitant presence in the same episode of psychomotor excitement and depression was originally classified by Kraepelin as a mixed episode. This view has been widely debated with some authors who agree that agitated depression is a mixed state [6] and others who argue that psychomotor agitation is just a manifestation of severe melancholia [7]. The nosological status of agitated depression is still unresolved and its nature is a matter of dispute [8], even if in the last decades a growing number of psychiatrists have considered agitated depression as a mixed state.

Koukopoulos and Koukopoulos [8] proposed that agitated (mixed) depression consisted in the presence of depressed mood associated with at least two symptoms among inner tension, psychomotor agitation (PA), and racing/crowded thoughts which worsened with AD treatment [9]. A recent study validated the diagnostic criteria proposed by Koukopoulos for mixed depression, corroborating their nosological validity [10]. Several reports indicate that agitated depression in MDEs could be related to the bipolar spectrum and more specifically to a bipolar mixed state, stressing the excitatory nature of such syndrome [11–14].

The aim of the present pooled post-hoc analysis was to further investigate PMSs in a large multinational sample of patients with MDE, comparing clinical features among patients with PA, PR, and patients without psychomotor symptoms (NPS) and focusing on the relationship between different psychomotor patterns, diagnostic and course characteristics.

Methods

The present pooled post-hoc analysis evaluated data from two international multicentre, non-interventional, cross-sectional studies, the BRIDGE [15] and the BRIDGE-II-MIX [16]. This is the first analysis based on a pooled cohort from BRIDGE and BRIDGE-II- MIX studies.

In summary, the BRIDGE (Bipolar Disorders: Improving Diagnosis, Guidance and Education) study was a large, cross-sectional diagnostic investigation of 5635 depressed patients conducted in 18 countries in Europe, Asia and North Africa, between April 2008 and May 2009. The BRIDGE study applied a descriptive, bottom-up approach to detect hypo/mania in patients with a MDE [15].

The BRIDGE-II-MIX Study [16] was a multicentre, international, non-interventional, cross-sectional study conducted between June 2009 and July 2010 in 239 centres in Bulgaria, Egypt, Morocco, Netherlands, Portugal, Russia, Spain and Turkey. A total of 2811 patients gave their written informed consent and provided complete data. The number of investigators per country ranged from 62 in Spain to 18 in Egypt. Each centre was expected to enrol 10 to 20 consecutive patients consulting for a MDE during a 3-months recruitment period. The primary objective of the BRIDGE-II-MIX study was to establish the frequency of depressive mixed states by analysing all the relevant symptoms of either pole.

Participants included in both cohorts were adults aged 18 or older, diagnosed with MDE according to DSM IV-TR diagnostic criteria at the time of the consultation. Patients presenting with an acute non-psychiatric condition were excluded.

The two samples were totally independent from each other. The two databases have been merged because similar in the methodology of investigation and the explored clinical variables.

The specific case report form (CRF) for each study have been independently revised by two investigators (CM and MB) and the variables assessing the same features in the two CRF have been selected for inclusion in the pooled dataset. Continuous variables, namely age and global assessment of functioning (GAF) score, similarly reported in both study have been merged. Age at first psychiatric symptom, age at first setting of depressive diagnosis, total number of mood and depressive episodes in the past, total number of hospitalizations, duration of the current episode, that were coded in ranges in the BRIDGE study, have been converted into the same ranges in the BRIDGE-II-MIX study in order to obtain a comparable ordinal variable between the datasets. The variables assessed only in one of the two samples, i.e. mixed features of the depressive episode, weight, height, smoking status, postpartum depression, clinical global impression (CGI) scale, illness progression (mood episodes with/without free intervals), all the items from the self-questionnaire assessing mixed features, have been excluded. The two databases have been merged using the specific SPSS tool and have been subsequently independently revised by two investigators (CM and MB).

Both studies were conducted according to the Declaration of Helsinki (Hong Kong Amendment), Good Epidemiologic Practice, and the International Epidemiological Association European Federation Guidelines for proper conduct of

epidemiologic research, as well as pertinent national legal and regulatory requirements. For both studies, written informed consent was obtained from each patient. The protocols have been submitted and approved by the appropriate local ethics committee in each country.

The sample consisted of 8496 patients with a MDE. Patients diagnosed with borderline personality disorder (BPD) (n=719) have been excluded from the analysis in order to control for the possible bias represented by PA as a trait-like characteristic of BPD. For the same reason, patients presenting Attention Deficit Hyperactivity Disorder comorbidity (n=88) have been excluded. Patients with anxiety disorders or alcohol/substance abuse may present psychomotor changes at certain stages of the disease, however we cannot assume that psychomotor symptoms are stable to such an extent they could represent a biasing factor. The final total sample of the present post-hoc analysis was composed by 7689 patients.

Data collection

For both studies, community and hospital-based psychiatrists recruited consecutively all eligible adult (18 years or older) patients with a diagnosis of MDE. Patients were assessed in a single visit by the participating psychiatrists with a structured protocol covering socio-demographic variables, clinical features, family history, treatment and comorbid psychiatric disorders. Psychiatric diagnoses were based on DSM-IV-TR. For a better detection of BD patients, criteria for bipolarity proposed by Angst et al. [17] were also used.

The presence of PA and PR has been clinically evaluated, according to the corresponding definitions of the DSM-IV-TR. PA is defined as the presence of excessive, non-productive and repetitious motor activity (such as restlessness, pacing, fidgeting, etc.) associated with a feeling of inner tension. Conversely, PR is a visible generalized slowing of movements and speech.

Bipolarity specifier criteria [15,18] attribute a diagnosis of BD in patients who experienced an episode of elevated mood, an episode of irritable mood, or an episode of increased activity with at least 3 of the symptoms listed under Criterion B of the DSM-IV-TR associated with at least 1 of the 3 following consequences: (1) unequivocal and observable change in functioning uncharacteristic of the person's usual behaviour, (2) marked impairment in social or occupational functioning observable by others, or (3) requiring hospitalization or outpatient treatment. No minimum duration of symptoms was required and no exclusion criteria were applied. Functional status was determined in both studies by the physician, using the GAF scale [19].

The evaluation protocol was explicitly structured to use skills that fully trained psychiatrists would have and routinely apply in conducting an initial evaluation of a patient. No rating scales requiring calibration with a standard were incorporated. The evaluators were instructed to follow their usual practice, as training might alter these practices and could represent a biasing factor.

Statistical analysis

Chi-square test was used for comparison between groups for categorical variables and ANOVA test with post-hoc Tukey comparison test for continuous variables. The bivariate analysis involved many tests of statistical significance, raising the problem of type I errors. For this reason, we corrected for multiple comparisons and utilized a Bonferroni-corrected threshold for statistical significance. Three stepwise backward logistic regression models were then used to identify the predictive value of the clinical characteristics on the presence of PA versus (vs.) PR, PA vs. NPS, PR vs. NPS. An alpha of 0.05 in the bivariate comparison was utilized as the cut-off for the inclusion of a variable in the regression model. The stepwise modelling procedure started with the full model and consisted, for each step, in eliminating the least statistically significant variable from the model and re-computing the revised model, until all remaining variables were at $p<0.1$. Odds ratios with 95% confidence intervals were used for observed associations. We used the statistical routines of SPSS Statistics 23.0 for Windows (SPSS Inc., USA).

Results

Focusing on Psychomotor patterns, we divided the whole sample of MDE patients (n=7689) into 3 subgroups: the PR group (n= 3720), the PA group (n=1971) and the NPS group (n=1998). We compared the 3 subgroups with each other, considering demographical and clinical variables such as age, gender, familial history of BD, clinical course of the illness, psychiatric comorbidity, GAF, previous treatments and diagnostic distribution of BD.

Comparisons between PR and NPS patients

PR and NPS subgroups did not show significant differences in gender distribution (female gender respectively, 66.8% and 64.8%) (Table 1). Conversely, PR patients showed significantly higher mean age at the moment of the evaluation (45.6 years old) than NPS patients (43.5 years old) (Table 2). The age at first MDE was similar in the two subgroups, while a higher rate of first-degree family history of BD was found within the PR patients in comparison to NPS patients (respectively, 14.7% and. 12.7%) (Table 1). PR subjects had also significantly higher rates of manic/hypomanic switches with ADs (17.6%) compared to the NPS group (14.3%). Likewise, PR patients had more frequently ≥3 lifetime MDEs (51.3% vs. 42.2%), atypical features (16.9% vs. 14.5%) and psychotic features (9.8% vs. 5.9%) than NPS patients. On the contrary, a history of suicide attempts and the rate of current MDE duration less than 1 month were similar in the two groups. No differences were found in the two groups regarding psychiatric comorbidities, such as anxiety disorders and alcohol-substance use disorders. Considering pharmacological treatments, PR patients were more frequently treated with antipsychotics (respectively 34.5% and 26%) and mood stabilizers (33% and 28.4%) than the NPS patients, while no significant differences were found for ADs use and ECT.

As for diagnostic distribution, 591 (15.9%) patients in the PR group and 242 (12.2%) patients in NPS group fulfilled DSM IV-TR criteria for BD, showing a statistically significant difference. When considering criteria for bipolarity proposed by Angst, we also found a significant difference between PR and NPS groups (respectively 42.8% and 38.6%).

The GAF score was significantly higher in the NPS group (mean 54.3, ds=14.4) than in the PR group (mean 51.0 ds=14.4) (Table 2).

In the multivariate logistic regression analysis, the variables significantly associated with PR were the higher mean age at the evaluation, a clinical history of 3 or more MDEs, psychotic features, previous treatment with antipsychotics, a lower global functioning, measured with the GAF scale, and a diagnosis of BD according to DSM-IV-TR criteria (Table 3).

Comparisons between PA and NPS

Gender distribution and mean age at the moment of evaluation were similar in PA and NPS subgroups (Table 1 and 2). We found significant differences regarding the early onset of the first MDE (<30 years old) in the PA patients compared to NPS patients (respectively 42.1% vs. 35.4%). Moreover, significant higher rates of first-degree family history of BD (19.3% vs. 12.7%), manic/hypomanic switches with ADs (21.5% vs. 14.3%), presence of atypical (20.0% vs. 14.5%) and psychotic (18.4% vs. 5.9%) features, ≥3 lifetime MDEs (48.9% vs. 42.2%), current MDE duration less than 1 month (34.1% vs. 29.8%) and history of suicide attempts (26.7% vs. 21.2%) were found in the PA group compared to NPS patients.

Regarding the presence of psychiatric comorbidities, patients in the PA group showed significantly higher rates of anxiety disorders (26.8% vs. 18.4) compared to the NPS group.

As for current treatments, we found a higher use of antipsychotics (38.2% vs. 26.0%), mood stabilizers (40.6% vs. 28.4%) and ECT (4.4% vs. 2.2%) in the PA group compared to the NPS group, whilst no significant differences were found amongst the two groups regarding ADs use. As for BD diagnosis, PA subjects fulfilled significantly more often DSM-IV criteria compared to NPS patients (respectively 18.6% vs. 12.2%). Likewise, PA patients showed higher rates of bipolarity, according to the criteria proposed by Angst et al. The global functioning was significantly lower in PA patients compared to NPS subjects.

In the multivariate logistic regression analysis, the clinical features that significantly differentiated PA from NPS patients were family history of BD, the presence of current atypical depression, psychotic features, comorbidity with anxiety disorders, treatment with antipsychotics and mood stabilizers, a diagnosis of BD according to DSM IV-TR criteria, along with lower GAF scores (Table 3).

Comparison between PA and PR

PA and PR patients differed significantly in terms of mean age at the index episode (respectively, 43.6 vs. 45.6), GAF score (49.9 vs. 51) (Table 2) and family history of BD (19.3% vs. 14.7%) (Table 1). Concerning clinical variables, significant differences were found amongst PA and PR patients in the early onset of the first MDE (respectively, 42.1% vs. 34.1%), the presence of manic/hypomanic switches with ADs (21.5% vs. 17.6%), atypical features (20.0% vs. 16.9%), psychotic features (18.4% vs. 9.8 %), the presence of lifetime suicide attempts (26.7% vs. 22.8%) and current episode duration less than 1 month (34.1% vs. 30.5%). The two groups did not differ as regard to the presence of ≥3 MDEs. Psychiatric comorbidities resulted to be significantly

higher in the PA group, showing higher rates of anxiety disorders (26.8% vs. 19.4%) and alcohol-substance use disorder (5.4% vs. 4.7%) in comparison to PR group. The two groups significantly differed regarding the use of antipsychotics, mood stabilizers and ECT that resulted more frequently administered in patients with PA compared to PR patients (respectively 38.2% vs. 34.5%, 40.6% vs. 33.0% and 4.4% vs. 2.6%). Regarding the diagnostic distribution in the two groups, PA and PR showed statistical difference if both DSM-IV criteria (18.6% vs. 15.9%) and criteria for bipolarity proposed by Angst (49.7% vs. 42.8%) are considered (Table 1).

Using multivariate logistic regression analysis, the characteristics significantly related to the presence of PA were early onset of first MDE, atypical depression, psychotic features, comorbidity with anxiety disorders, treatment with mood stabilizers and ECT as well as the presence of Angst's specifier for bipolarity (Table 3).

Discussion

In this pooled post-hoc analysis of BRIDGE and BRIDGE-II-MIX studies, our results indicate that PMSs represent common clinical features during a MDE, occurring in almost three out of four patients, as reported in previous studies [20].

Several findings from the present study seem to support our expected hypothesis of the inclusion of patients with PMSs (PA and PR) within the rubric of BD. First, we found significantly higher rates of BD diagnosis in the PA and PR groups compared to the NPS group using both DSM IV-TR and bipolar specifier criteria. Moreover, the PA and PR groups reported higher frequencies of clinical and course variables, such as family history for BD, manic/hypomanic switches induced by ADs, atypical features,

psychotic features and higher rates of more than 3 lifetime MDEs, which have been recognized as the most relevant clinical indicators of bipolarity in depressed patients [15,17,21,22]. By comparing the two "psychomotor" subgroups (PA and PR), we found that patients with agitated depression presented more frequently most of the clinical and course variables associated with a "bipolar diathesis", such as a family history of BD, manic/hypomanic switches with ADs, atypical and psychotic features.

Furthermore, the PA group was significantly associated with an early onset of first MDE and with a worse course of illness compared to PR and NPS groups. In fact, PA patients presented more often anxiety and alcohol-substances use comorbidities along with higher frequencies of suicide attempts, indicating a more severe and difficult-to-treat subtype of patients. The role of PA in suicidal behaviours has been investigated in several studies highlighting the relationship between anxiety, psychomotor activation, suicide attempts and the mixed element during a MDE [13,23–25]. In this context, PA might be considered as a core dimension in depressed patients with mixed features and it could be seen as a part of the construct associated with suicidal behaviours in depressed BD and major depressive disorder patients. Noteworthy, despite several previous studies emphasized the importance of PA as a mixed element, associated with an increased risk of suicide behaviours [25], currently PA is not included among the criteria for "mixed features" specifier for a depressive episode in DSM-5.

Interestingly, we found a broadly more severe impairment in the global functioning among patients with PMSs compared to the NPS group. This is in agreement with previous studies that highlighted a globally more severe impact on psychosocial functioning in patients with PMSs, without however distinguishing

between retardation and agitation [26]. In our post-hoc analysis, the PA group showed significantly lower mean GAF scale scores compared with the PR group, indicating a poorer functional outcome in this subgroup of patients.

It is noteworthy that in our sample, the PA and PR groups compared with the NPS group, and the PA group compared separately with the PR group, had higher frequency of antipsychotics and mood stabilizers use, reinforcing the hypothesis of a greater association of PMSs with bipolarity and treatment complexity [27]. After multiple logistic regressions, we found that treatment with mood stabilizers was mostly predicted by the presence of PA, possibly indicating a stronger association of bipolarity features with this depressive subtype. In other words, patients with PA seem to belong to a difficult-to-treat subgroup of depressed patients that require more complex pharmacological treatment. In the same line is the observation that ECT, frequently used in treatment-resistant depression, resulted to be more frequently used in patients with PA than in the other groups.

In the multiple logistic regression models, the presence of psychotic symptoms, the DSM IV-TR diagnosis of BD and the impairment in global functioning predicted both PA and PR. Interestingly, the variables that significantly differentiated PA from PR were some of the clinical features most associated with a bipolar diathesis, such as early onset of first MDE, atypical depressive features, psychotic features and a higher BD diagnosis according to the bipolar specifier [18]. These results corroborate the evidence for the association between MDE with PMSs and bipolarity. Furthermore, among the depressive syndromes with PMSs, those characterized by PA are the most closely related to bipolarity and seem to belong to a difficult-to-treat subgroup, requiring more complex regimen of pharmacological treatment.

Historically, MDEs with psychomotor agitation were classified by Kraepelin among the depressive forms of mixed state and characterized by the contemporary presence of depressive symptoms and different elements of psychomotor excitement [28,29]. Although the classification of agitated depression is still a matter of debate, in the last decades a growing number of studies supported the view that agitated depression is more closely aligned with the mixed phase of BD [23,30,31]. In this vein, a possible alternative interpretation of our results is that the presence of PA in depressive states contradicts the bipolar/unipolar distinction. As Kraepelin [28] and Koukopoulos [9] held, mixed states are actually very common and thus it is not feasible to divide mood disorders into bipolar and unipolar types. "Manic-depressive illness" should be viewed as a continuum of forms that presents either as depression or mania or, most commonly, both.

The principal strengths of the present post-hoc analysis include the large sample size, obtained by pooling BRIDGE and BRIDGE-II -MIX cohorts, and the wide range of worldwide care settings encompassed. The studies included hospital and community psychiatrists [15,16]. This broad, local clinical practice–relevant sample likely increases the generalizability of the findings. One limitation is that the participating centres were not randomly selected, which may have led to a bias through the inclusion of psychiatrists with a particular interest in BD who, as a result, look more carefully for psychomotor symptoms and are more likely to rate them as such. This may be seen, however, as a positive point, in the sense that some expertise is needed to detect past hypomanic symptoms and psychomotor abnormalities. Notwithstanding this, a random selection of participants would not have been possible because lists of all practicing physicians were not in the public domain for the participating countries. Another limitation is the widely varying rates of hospitalized patients across countries, ranging from 11.9% to 73.7%

(BRIDGE) and from 1.0% to 57.8% (BRIDGE-II-MIX), which reflect clinical practices in the respective countries, and hospitalization rates were not associated with significant differences in rates of PMS. Finally, in the present study, the possible role of pharmacological treatments in the induction of PMS has not been directly evaluated, however the association of PA with increased rate of antipsychotic and mood stabilizer drugs seems to suggest a minor influence of treatments on PMS.

In conclusion, our results seem to support the hypothesis that the presence of different patterns of PMSs during a MDE has important diagnostic, prognostic and therapeutic implications with a possible discriminative validity for distinguishing bipolar from unipolar depression. In addition, our study shows some important clinical and course differences between patients with psychomotor agitation and retardation, possibly suggesting the need to modify the DSM-5 diagnostic criteria for MDE which currently merge into a single criterion the two different motor patterns.

Acknowledgements

We thank for the support: the Spanish Ministry of Economy and Competitiveness integrated into the Plan Nacional de I+D+I and co-financed by the ISCIII-Subdirección General de Evaluación and the Fondo Europeo de Desarrollo Regional (FEDER); the Instituto de Salud Carlos III that supported this work through a "Río Hortega" contract (CM17/00258) to NV); the CIBERSAM (Centro de Investigación Biomédica en Red de Salud Mental); the Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement (2017_SGR_1365) and the CERCA Programme / Generalitat de Catalunya; the National Institute for Health Research (NIHR) Biomedical research Centre at South London and Maudsley NHS FoundationTrust and King's College London.

Funding/support:

Sponsored by Sanofi-Aventis. All investigators recruited received fees from the sponsor in recognition of their participation in the study on a per-patient basis. Sanofi-Aventis was involved in both the study design (BRIDGE and BRIDGE-II-MIX), conduct, monitoring and preparation of the two final databases, but had no influence on the pooled database nor on the final data analysis of this report.

This report represents independent research funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

This report represents independent research funded by the Instituto de Salud Carlos III that supported this work through a "Río Hortega" contract (CM17/00258) to NV.

Declaration of Interest

Dr. Mainardi declares no conflict of interest and reports no financial or other relationship relevant to the subject of this article.
Dr. Pacchiarotti has received CME-related honoraria, or consulting fees from ADAMED, Janssen-Cilag and Lundbeck and reports no financial or other relationship relevant to the subject of this article.
Dr. Verdolini is funded by the Spanish Ministry of Economy and Competitiveness, Instituto de Salud Carlos III through a "Río Hortega" contract (CM17/00258) and reports no financial or other relationship relevant to the subject of this article.
Dr. Barbuti declares no conflict of interest and reports no financial or other relationship relevant to the subject of this article.
Dr. Maccariello declares no conflict of interest and reports no financial or other relationship relevant to the subject of this article.
Prof. Angst declares no conflict of interest and reports no financial or other relationship relevant to the subject of this article.

Prof. Azorin has received research support and has acted as a consultant and/or served on a speaker's bureau for Janssen, Lundbeck, Otsuka, Roche, Servier and Takeda, and reports no financial or other relationship relevant to the subject of this article.

Prof. Bowden has received grant support from Sunovion and the NIMH, and has consulted for Takeda, and reports no financial or other relationship relevant to the subject of this article.

Prof. Mosolov has received research grants from, and been involved in clinical trials for Servier, Eli Lilly, Lundbeck, AstraZeneca, Janssen-Cilag, Sanofi-Aventis and Geodon Richter and reports no financial or other relationship relevant to the subject of this article.

Prof. Young is honorary Consultant SLaM (NHS UK). He provided lectures and advisory boards for the following companies with drugs used in affective and related disorders: Astrazenaca, Eli Lilly, Janssen, Lunbeck, Sunovion, Servier, Livanova, Janssen. He does not share holdings in pharmaceutical companies. He is Lead Investigator for Embolden Study (AZ), BCI Neuroplasticity study and Aripiprazole Mania Study, he did investigator initiated studies from AZ, Eli Lilly, Lundbeck, Wyeth. Grant funding (past and present): NIMH (USA); CIHR (Canada); NARSAD (USA); Stanley Medical Research Institute (USA); MRC (UK); Wellcome Trust (UK); Royal College of Physicians (Edin); BMA (UK); UBC-VGH Foundation (Canada); WEDC (Canada); CCS Depression Research Fund (Canada); MSFHR (Canada); NIHR (UK). Janssen (UK). He reports no financial or other relationship relevant to the subject of this article.

Prof. Vieta has received research support from or served as consultant, adviser or speaker for AB-Biotics, Actavis, Allergan, Angelini, AstraZeneca, Bristol-Myers Squibb, Dainippon Sumitomo Pharma, Ferrer, Forest Research Institute, Gedeon Richter, Glaxo-Smith-Kline, Janssen, Lundbeck, Otsuka, Pfizer, Roche, Sanofi-Aventis, Servier, Shire, Sunovion, Takeda, Telefónica, the Brain and Behaviour Foundation, the Spanish Ministry of Science and Innovation (CIBERSAM), the Seventh European Framework Programme (ENBREC), and the Stanley Medical Research Institute and reports no financial or other relationship relevant to the subject of this article.

Prof. Perugi has acted as consultant of Lundbeck, Angelini, FB-Health. He received grant/research support from Lundbeck and Angelini. He is on the speaker/advisory board of Sanofi-Aventis, Lundbeck, FB-Health, Angelini, and reports no financial or other relationship relevant to the subject of this article.

References

1. Schrijvers D, Hulstijn W, Sabbe BGC. Psychomotor symptoms in depression: A diagnostic, pathophysiological and therapeutic tool. J Affect Disord. 2008;109(1-2):1-20.
2. Parker G, Roy K, Wilhelm K, Mitchell P, Hadzi-Pavlovic D. The nature of bipolar depression: implications for the definition of melancholia. J Affect Disord. 2000;59(3):217-224.
3. Parker G, Fink M, Shorter E, et al. Issues for DSM-5: Whither Melancholia? The Case for Its Classification as a Distinct Mood Disorder. Am J Psychiatry. 2010;167(7):745-747.
4. Leonpacher AK, Liebers D, Pirooznia M, et al. Distinguishing bipolar from unipolar depression: the importance of clinical symptoms and illness features. Psychol Med. 2015;45(11):2437-2446.
5. Hantouche EG, Akiskal HS. Bipolar II vs. unipolar depression: psychopathologic differentiation by dimensional measures. J Affect Disord. 2005;84(2-3):127-132.
6. Dreyfus GL. Die Melancholie, Ein Zustandsbild Des Manisch-de- Pressiven Irreseins. Jena, Germany: Fischer; 1907.
7. Stransky E. Das manisch-depressive Irresein. 1911.
8. Koukopoulos A, Koukopoulos A. Agitated depression as a mixed state and the problem of melancholia. Psychiatr Clin North Am. 1999;22(3):547-564.
9. Koukopoulos A, Sani G, Koukopoulos AE, Manfredi G, Pacchiarotti I, Girardi P. Melancholia agitata and mixed depression. Acta Psychiatr Scand. 2007;115(s433):50-57.
10. Sani G, Vöhringer PA, Napoletano F, et al. Koukopoulos′ diagnostic criteria for mixed depression: A validation study. J Affect Disord. 2014;164:14-18.
11. Perugi G, Akiskal HS, Micheli C, Toni C, Madaro D. Clinical characterization of depressive mixed state in bipolar-I patients: Pisa-San Diego collaboration. J Affect Disord. 2001;67(1-3):105-114.
12. Faedda GL, Marangoni C, Reginaldi D. Depressive mixed states: A reappraisal of Koukopoulos′criteria. J Affect Disord. 2015;176:18-23.
13. Pacchiarotti I, Nivoli AMA, Mazzarini L, et al. The symptom structure of bipolar acute episodes: In search for the mixing link. J Affect Disord. 2013;149(1-3):56-66.
14. Iwanami T, Maeshima H, Baba H, et al. Psychomotor agitation in major depressive disorder is a predictive factor of mood-switching. J Affect Disord. 2015;170:185-189.
15. Angst J, Azorin JM, Bowden CL, et al. Prevalence and characteristics of undiagnosed bipolar disorders in patients with a major depressive episode: The BRIDGE study. Arch Gen Psychiatry. 2011;68(8):791-799.
16. Perugi G, Angst J, Azorin JM, et al. Mixed features in patients with a major depressive episode: The BRIDGE-II-MIX Study. J Clin Psychiatry. 2015;76(3):e351-e358.
17. Angst J, Gamma A, Bowden CL, et al. Diagnostic criteria for bipolarity based on an international sample of 5,635 patients with DSM-IV major depressive episodes. Eur Arch Psychiatry Clin Neurosci. 2012;262(1):3-11.
18. Angst J, Gamma A, Benazzi F, Ajdacic V, Eich D, Rössler W. Toward a re-definition of subthreshold bipolarity: epidemiology and proposed criteria for bipolar-II, minor bipolar disorders and hypomania. J Affect Disord. 2003;73(1-2):133-146.

19. Endicott J, Spitzer RL, Fleiss JL, Cohen J. The global assessment scale. A procedure for measuring overall severity of psychiatric disturbance. Arch Gen Psychiatry. 1976;33(6):766-771.
20. Maj M, Pirozzi R, Magliano L, et al. Agitated "Unipolar" Major Depression: Prevalence, Phenomenology, and Outcome. J Clin Psychiatry. 2006;67(5):712-719.
21. Barbuti M, Pacchiarotti I, Vieta E, et al. Antidepressant-induced hypomania/mania in patients with major depression: Evidence from the BRIDGE-II-MIX study. J Affect Disord. 2017;219:187-192.
22. Vieta E, Salagre E, Grande I, et al. Early Intervention in Bipolar Disorder. Am J Psychiatry. 2018;1(175):411-426.
23. Akiskal HS, Benazzi F, Perugi G, Rihmer Z. Agitated "unipolar" depression re-conceptualized as a depressive mixed state: Implications for the antidepressant-suicide controversy. J Affect Disord. 2005;85(3):245-258.
24. Azorin J-M, Kaladjian A, Adida M, et al. Self-assessment and characteristics of mixed depression in the French national EPIDEP study. J Affect Disord. 2012;143(1-3):109-117.
25. Popovic D, Vieta E, Azorin JM, et al. Suicide attempts in major depressive episode: Evidence from the BRIDGE-II-Mix study. Bipolar Disord. 2015;17(7):795-803.
26. Burdick KE, Gunawardane N, Goldberg JF, Halperin JM, Garno JL, Malhotra AK. Attention and psychomotor functioning in bipolar depression. Psychiatry Res. 2009;166(2-3):192-200.
27. Vieta E, Valentí M. Pharmacological management of bipolar depression: Acute treatment, maintenance, and prophylaxis. CNS Drugs. 2013;27(7):515-529.
28. Angst J, Sellaro R. Historical perspectives and natural history of bipolar disorder. Biol Psychiatry. 2000;48(6):445-457.
29. Marneros A. Origin and development of concepts of bipolar mixed states. J Affect Disord. 2001;67(1-3):229-240.
30. Swann AC. Activated Depression: Mixed Bipolar Disorder or Agitated Unipolar Depression? Curr Psychiatry Rep. 2013;15(8):376.
31. Benazzi F, Koukopoulos A, Akiskal HS. Toward a validation of a new definition of agitated depression as a bipolar mixed state (mixed depression). Eur Psychiatry. 2004;19(2):85-90.

Table 1. Clinical Features in 7689 patients with Major Depressive Episode (MDE): comparisons among patients with Psychomotor Agitation (PA), with Psychomotor Retardation (PR) and without motor symptoms (NPS).

	PR n=3720 (48.4%)	PA n=1971 (25.6%)	NPS n=1998 (26%)	PR vs. NPS OR (95% CI)	PA vs. NPS OR (95% CI)	PA vs. PR OR (95% CI)
Female gender	2478 (66.8%)	1262 (64.2%)	1289 (64.8%)	1.09 (.98-1.23)	.98 (.86-1.11)	.89 (.80-1.00)
First MDE <30 years	1257 (34.1%)	824 (42.1%)	698 (35.4%)	.94 (.84-1.06)	1.33 (1.17-1.51)	1.40 (1.26-1.57)
First MDE >60 years	157 (4.3%)	67 (3.4%)	86 (4.4%)	.98 (.75-1.28)	.78 (.56-1.07)	.80 (.56-1.07)
First-degree Family History BD	540 (14.7%)	375 (19.3%)	250 (12.7%)	1.18 (1.01-1.39)	1.65 (1.38-1.96)	1.39 (1.20-1.61)
Manic/hypomanic switch with AD	629 (17.6%)	399 (21.5%)	270 (14.3%)	1.28 (1.09-1.49)	1.64 (1.38-1.94)	1.28 (1.11-1.48)
Atypical features	627 (16.9%)	394 (20.0%)	289 (14.5%)	1.2 (1.03-1.39)	1.48 (1.25-1.74)	1.23 (1.07-1.42)
Psychotic features	363 (9.8%)	362 (18.4%)	118 (5.9%)	1.72 (1.39-2.14)	3.59 (2.82-4.46)	2.08 (1.78-2.44)
3 or more MDEs	1901 (51.3%)	960 (48.9%)	841 (42.2%)	1.44 (1.3-1.61)	1.31 (1.15-1.48)	.91 (.81-1.01)
Current episode <1 month	1116 (30.5%)	662 (34.1%)	583 (29.8%)	1.03 (.92-1.17)	1.22 (1.06-1.39)	1.18 (1.05-1.32)
Suicide attempts	848 (22.8%)	525 (26.7%)	424 (21.2%)	1.1 (.96-1.25)	1.35 (1.16-1.56)	1.23 (1.08-1.57)
Psychiatric comorbidity						
Anxiety Disorders	717 (19.4%)	525 (26.8%)	364 (18.4%)	1.07 (.93-1.23)	1.63 (1.4-1.9)	1.52 (1.34-1.73)
Alcohol-substance Use Dis.	175 (4.7%)	106 (5.4%)	80 (4.1%)	1.17 (.89-1.54)	1.35 (1.0-1.81)	1.15 (0.9-1.60)
Treatment						
ADs	3272 (88.0%)	1727 (87.6%)	1758 (88.0%)	.99 (.84-1.18)	.97 (.80-1.17)	.97 (.82-1.14)
Antipsychotics	1282 (34.5%)	773 (38.2%)	520 (26.0%)	1.49 (1.32-1.69)	1.83 (1.6-2.1)	1.23 (1.1-1.37)
Mood-stabilizers	1228 (33.0%)	800 (40.6%)	567 (28.4%)	1.24 (1.1-1.4)	1.72 (1.51-1.97)	1.39 (1.24-1.55)
ECT	96 (2.6%)	87 (4.4%)	43 (2.2%)	1.2 (.84-1.73)	2.1 (1.45-3.04)	1.74 (1.30-2.34)
Diagnostic distribution of BD						
BD (DSM-IV-TR)	591 (15.9%)	364 (18.6%)	242 (12.2%)	1.36 (1.16-1.6)	1.64 (1.38-1.97)	1.21 (1.04-1.39)
BD (Specifier)	1591 (42.8%)	976 (49.7%)	771 (38.6%)	1.19 (1.06-1.33)	1.57 (1.38-1-78)	1.32 (1.18-1.47)
BD (DSM-IV-TR and Specifier)	455 (12.3%)	312 (15.9%)	194 (9.8%)	1.29 (1.08-1.54	1.75 (1.44-2.12)	1.36 (1.16-1.59)

Notes; **BD**, Bipolar Disorder; **AD**, Antidepressant; **ECT**, Electroconvulsive therapy, **DSM**, Diagnostic and Statistical Manual of Mental Disorders.

Table 2. ANOVA univariata test for age at clinical evaluation and Global Assessment of Functioning (GAF) score in patients with Psychomotor Agitation (PA), Psychomotor Retardation (PR) and without motor symptoms (NPS).				
	PA	**PR**	**NPS**	**p**
GAF mean; (sd)	49.9 (14.5)	51.0 (14.4)	54.3 (13.5)	<0.001
Age mean; (sd)	43.6 (13.6)	45.6 (13.9)	43.5 (13.5)	<0.001
Post-hoc comparisons using the Tukey test				
GAF: NPS > PR > PA	NPS > PR (3.332, 95%-CI [2.4-4.26]) NPS > PA (4.415, 95%-CI [3.35-5.48]) PR > PA (1.083, 95%-CI [0.15-2.01])			
Age: PR > NPS > PA	PR > NPS (2.049, 95%-CI [1.16-2.94]) PR > PA (1.996 95%-CI [1.1-2.89]) NPS > PA (0.53, 95%-CI [-1.08-0.97])			

Table 3. Multivariate logistic regression model backward procedure of clinical variables associated with psychomotor patterns in patients with MDE

	PR vs NPS* OR (95% CI)	PA vs NPS† OR (95% CI)	PA vs PR‡ OR (95% CI)
Age	**1.01 (1.00-1.01)**	-	0.99 (1.0-1.38)
Female gender	-	-	
First MDE <30 years	-	-	**1.19 (1.02-1.38)**
First MDE >60 years	-	-	-
First-degree family history of BD	-	**1.29 (1.06-1.57)**	1.15 (0.98-1.35)
Manic/hypomanic switches with ADs	-	-	-
Atypical features	-	**1.41 (1.17-1.70)**	**1.18 (1.01-1.38)**
Psychotic features	**1.30 (1.03-1.64)**	**2.47 (1.93-3.16)**	**1.95 (1.65-2.31)**
3 or more MDEs	**1.22 (1.08-1.38)**	-	-
Current episode <1 month	-	-	-
Suicide attempts	-	-	-
Anxiety disorders	-	**1.66 (1.41-1.96)**	**1.52 (1.32 -1.74)**
Alcohol-substance use disorder	-	-	-
ADs	-	-	-
Antipsychotics	**1.28 (1.12-1.46)**	**1.32 (1.12-1.54)**	-
Mood-stabilizers	-	**1.33 (1.13-1.55)**	**1.2(1.05-1.37)**
ECT	-		**1.64 (1.18- 2.29)**
Bipolar Disorder (DSM-IV-TR)	**1.21 (1.02-1.43)**	**1.22 (0.99-1.50)**	-
Bipolar Disorder (Specifier)	-	-	**1.13 (1.00-1.30)**
GAF	**0.99 (0.98-0.99)**	**0.99 (0.98- 0.99)**	-

NPS, no psychomotor symptoms; **PA**, Psychomotor Agitation; **PR**, Psychomotor Retardation; **MDE**, Major Depressive Episode**; BD**, Bipolar Disorder; **AD**, Antidepressant; **ECT**, Electroconvulsive therapy; **DSM**, Diagnostic and Statistical Manual of Mental Disorder; **GAF**, Global Assessment of Functioning;

*Chi-square= 134,598, df=6; p<0.001; variables not in the equation: mood-stabilizers, manic/hypomanic switches with ADs, atypical features, first degree family history of BD.

†Chi-square= 134,598 df=8; p<0.001; variables not in the equation: manic/hypomanic switches with ADs, current episode<1month, suicide attempts, 3 or more MDEs, first MDE<30 years, ECT.

‡Chi-square=189,051, df=9; p<0.001; variables not in the equation: GAF, manic/hypomanic switches with ADs, antipsychotics, current episode<1month, age, bipolar disorder (DSM IV TR), suicide attempts.